Avian Analgesia

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RECOGNIZING PAIN IN BIRDS

All vertebrate animals share similar neuroanatomic and neuropharmacologic components required for nociception, detection, transmission, and response to noxious stimuli. Pain is the sensory and emotional experience associated with actual or potential tissue damage. Pain affects the animal's physiology and behavior to reduce or avoid the damage, to reduce the likelihood of recurrence and to promote recovery. Assessment of pain must account for species, gender, age, strain, environment, and concurrent disease. The type of pain such as acute, chronic, somatic, visceral, clinical, or neuropathic also affects the behavior of the bird. Pain is subjective and the emotional component is difficult for us to translate because most avian species lack facial expression and do not share verbal language with humans. In humans, we accept that pain is what the patient says it is, but with birds, people's perceptions of the bird's behavior determines what is recognized as pain.

Species variability occurs because of differences in pain sensitivity, the conscious response to pain, and the physiologic response to analgesic therapy. Genetic variability with response to pain has been demonstrated at the individual level and in different strains of chickens.[1,2] Behavioral changes can be very cryptic and subtle but are often the earliest signs of pain detected by animal care staff or owners. Behavioral change does not manifest uniformly among different species of birds and observers must be familiar with the full range of normal behaviors for the species as well as the individual. It is important to observe birds at appropriate times for each species; for example, observing nocturnal species at night. Without knowing the range of normal behavior, an observer will find it extremely difficult to detect abnormal behavior, especially in prey species, which often only demonstrate cryptic and subtle changes. The outward behavior of a companion bird acclimated to handling does not accurately reflect the physiologic changes occurring with stress-related hormones, respiratory rate, or body temperature.[3,4] Therefore it can be inferred that a bird in pain may also mask physiologic changes associated with the pain.

Certain behaviors have evolved over thousands of years and have survival value; for example, immobility is a common behavior displayed by birds when being observed or

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examined, making pain evaluation challenging.[5] In chickens, crouching immobility has been associated with prolonged pain, stress, and fear responses. When a noxious stimulus was applied to ulcerated buccal lesions, chickens remained motionless in a crouchlike stance with the head pulled into the body and had significantly fewer alert head movements.[6] Removal of feathers from chickens caused a progression of behavioral changes from an alert agitated response following the initial removal of feathers to periods of crouching immobility following successive removal.[7]

Feather grooming is an avian behavior that runs the full spectrum of change associated with pain, both acute and chronic. Grooming activity may decrease when a bird is painful, but conversely over-grooming and feather destructive behaviors have been associated with chronic pain. In a social species housed with a group, a painful bird frequently isolates itself from the others, may sleep apart from the rest of the flock, and mutual grooming is often decreased.[4] In some species a display of discomfort, illness, or weakness may gain support or protection from conspecifics, but similar behavior in another species may attract attention from predators, or lower its status in the flock's social order.[8] Increased grooming activities to themselves or other birds can be an intentional distraction. Studies using chickens with experimental arthritis demonstrated that shifting attention can reduce painful behaviors and potentially reduce peripheral inflammation.[9]

Treating avian pain is limited by the reliability of pain assessment, which remains highly subjective, and clinicians often need to rely on indirect measures of pain. Having an identified behavior or set of behaviors that correlate with pain provides a response that can be used to monitor analgesic therapy. It is difficult to state when a bird's condition is effectively treated if it cannot be measured before and after therapy. Nonetheless, having an identified behavior or set of behaviors that correlate with pain provides a means to monitor response to pain treatment. Pain scales and score sheets are increasingly being used to assess pain in animals, especially when specifically designed for a given species under well-defined conditions. Using pain scales requires understanding of normal and pain-related behaviors for the species and individual under study. Pain score sheets can help maximize the efficacy of pain scoring using behavioral analysis. Score sheet descriptions of behavior must be refined, and terms must be clearly defined to reduce observer bias and interobserver variability. Once such a system is implemented, well-trained non-veterinary staff can perform scoring. These pain scales take time and effort to design.

Pain is not just a yes/no response, it occurs along a gradient. In lieu of species-specific pain score sheets for birds, there is tremendous value in using a generic pain scale of 1 to 10 to evaluate a bird's pain and the response to treatment and recovery from a painful condition. In a study completed by one of the authors, pigeons were evaluated after orthopedic surgery using a detailed numeric rating scale plus a simple 1 to 10 pain scale and there was significant correlation between both methods (J. Paul-Murphy, personal communication, July 1, 2010). Effective analgesia is expected to show a marked, easily discernable change in posture or behaviors that will effect a reliable change in the subjective pain score. If no change in pain score occurs, then the drugs, dose, or frequency of administration need to be reevaluated for that individual patient.

EVALUATION OF ANALGESICS

It is difficult to define and recognize when birds feel pain, and it can be even more challenging to objectively determine whether a pain medication is effective in the avian patient. To determine the efficacy of an analgesic in any species, it is important to determine the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug in that species. Integrating PK and PD data can also provide a basis for selecting clinically relevant dosing schedules for subsequent evaluation in disease models and clinical trials.[10] When the same dose produces different plasma concentrations in different species of birds, the variance is due to PK. When the same plasma concentration produces different responses in different species, the variance is due to PD. PK studies of analgesic drugs are insufficient to determine appropriate doses and dosing frequencies as plasma concentrations of opioids and nonsteroidal antiinflammatory drugs (NSAIDs) do not always correlate with delivery of analgesia. Plasma concentrations provide guidance for dosing frequencies, but it has been shown that duration of analgesic effect of a NSAID may be longer than predicted from plasma levels. The PK of analgesics vary considerably across all species that have been studied, so extrapolating clinical doses and dosing intervals from one species to another species is not appropriate. To date, very few PK studies have been published for analgesics in birds (**Tables 1** and **2**).

Anesthetic sparing studies provide an in vivo PD technique for objective evaluation by measuring the reduction in the amount of inhaled anesthetic capable of maintaining a minimal level of anesthesia following administration of the analgesic under investigation. This type of testing has been used in many species to evaluate analgesic drug properties, particularly opioids. Although this approach provides meaningful information, there are limitations because the anesthetic itself can be a confounding variable and when evaluating opioids it is difficult to assess whether an observed effect is an analgesic or a sedative response to the drug.

Assessing the inhibition of serum inflammatory markers may be useful for evaluating one aspect of NSAID analgesia, but serum concentrations of markers do not give a complete picture of the effect because many inflammatory markers are found at the site of inflammation rather than in serum. Acute inflammation models have been developed in many species by injecting irritating materials into tissues and measuring inflammatory factors in exudates for differences with and without the NSAID. Avian patients most commonly produce caseous exudates, making it difficult to collect and evaluate peripheral inflammatory markers for evaluation of NSAIDs. Inflammatory models are also used to create painful conditions with repeatable behaviors or weight bearing that can be quantified such as acute synovitis/arthritis models in chickens and parrots.[16,18,20,24,26,34] In one model the injection of urate microcrystals into the intertarsal joint caused acute inflammatory arthritis leading to measurable changes in weight bearing and lameness. A study with Amazon parrots differentiated significant improvement in weight bearing when birds were given butorphanol versus less improvement in the same birds given carprofen.[26] Evaluating the response of a bird to a painful stimulus, also termed noxious stimulus, with and without analgesics is used to determine efficacy when behavioral responses or thresholds can be measured. The noxious stimuli used in avian analgesia studies are variable but usually include withdrawal thresholds to thermal, electrical, or pressure stimuli. Experimental models have been developed in chickens and parrots but these models may not extrapolate to pain behaviors relevant to clinical pain. Therefore, the doses and dosing frequencies recommended in the published reports should always be critically evaluated case by case when clinically applied.

PREVENTIVE OR PREEMPTIVE ANALGESIA

Recent evidence suggests that surgical incision and other painful procedures in humans may induce prolonged changes in the central nervous system (CNS) that later

Table 1
Opioid analgesics evaluated in avian species by either pharmacokinetic (PK) or pharmacodynamic (PD) studies

Drug	Dosage (mg/kg, unless noted)	Route	Frequency	Species	Comments	Type of Study	References
Butorphanol	0.5	IM, IV (median ulnar v; medial metatarsal v)	Single injection	Red-tailed hawks Great-horned owls	$t_{1/2}$ IV, IM very short (approx. 1–2 h); significantly more rapid clearance and shorter $t_{1/2}$ when given IV medial metatarsal than IV median ulnar v	PK	[11]
	5	Oral	Single dose	Hispaniolan Amazon parrots	Oral bioavailability<10%; do not recommend this route of administration	PK	[12]
	2–5	IM	Single injection	Hispaniolan Amazon parrots	PK: low mean plasma concentrations at 2 h after injection PD: withdrawal thresholds to electrical stimuli reduced after 2 mg/kg IM	PK/PD	[13]
	1	IM	Single injection	Cockatoos African gray parrots Blue-fronted Amazon parrots	Isoflurane-sparing study showed significant reduction in isoflurane MAC in the cockatoos and African grays, but not Amazon parrots	PD	[14,15]
	1–2	IM	Single injection	African gray parrots	Electrical stimuli to assess withdrawal thresholds; more significant reduction of withdrawal response at 2 mg/kg	PD	[16]
	3–6	IM	Single injection	Hispaniolan Amazon parrots	Electrical stimuli to assess withdrawal thresholds; 3 and 6 mg/kg effective	PD	[16]
	2	IM	Single injection	Hispaniolan Amazon parrots	Safe and effective preemptive analgesia with sevoflurane anesthesia for endoscopy	PD	[17]

Fentanyl	0.02 0.2	IM SC	Single injection	Cockatoos	PK: rapid absorption and elimination PD: withdrawal thresholds to electrical and thermal stimuli. 0.02 mg/kg did not affect either threshold; 0.2 mg/kg did affect both withdrawal thresholds but only some birds; hyperactivity in first 15–30 min	PK/PD	[18]
	0.15–0.50 μg/kg/min	IV	Constant-rate infusion	Red-tailed hawks	Reduced isoflurane MAC 31%–55% in a dose-related manner, without significant effects on heart rate, blood pressure, Pa_{CO_2}, or Pa_{O_2}	PD	[19]
	0.05–1.0	Intraarticular	Single injection	Chickens	No significant effect on induced arthritis	PD	[20]
Buprenorphine	0.1	IM	Single injection	African gray parrots	PK: may not achieve effective plasma concentrations at this dose PD: no change in withdrawal response to noxious stimuli	PK/PD	[16,21]
	0.25 0.5	IM	Single injection	Domestic pigeons	Increased latency period for withdrawal from a noxious electrical stimulus of 2 h at 0.25 mg/kg and for 5 h for 0.5 mg/kg	PD	[22]
	0.05–1.0	Intraarticular	Single injection	Chickens	No significant effect on induced arthritis	PD	[20]
Nalbuphine	12.5 25 50	IM	Single injection	Hispaniolan Amazon parrots	PK: $t_{1/2}$ IM and IV less than 0.35 h Excellent IM bioavailability PD: 12.5 mg/kg produced 3 h analgesia; higher doses did not increase analgesic time	PD	[23]

Abbreviations: CR, care report or case series; IM, intramuscularly; IV, intravenously; PD, pharmacodynamic; PK, pharmacokinetic; TOX, toxicity; $t_{1/2}$, half-life; v, vein.

Table 2
NSAIDs evaluated in avian species by either pharmacokinetic (PK), pharmacodynamic (PD) evaluations, toxicologic (TOX) or clinical studies

Drug	Dosage (mg/kg)	Route	Frequency (Every hour)	Species	Comments	Type of Study	References
Sodium salicylate	100–200	IM	Single injection	Chickens	Arthritis painful behaviors partially reduced 1 h after ASA treatment	PD	24
	25	IV	Single injection	Chickens, ostrich, ducks, turkeys, pigeons	Rapid clearance except long $t_{1/2}$ in pigeon	PK	25
Carprofen	30	IM	Single injection	Chickens	Arthritis painful behaviors reduced 1 h after treatment	PD	24
	3	IM	12	Hispaniolan Amazon parrots	Arthritis pain partially reduced, effect less than 12 h	PD	26
	1	IM	Single injection	Chickens	Improved locomotion of lame birds 1 h after treatment	PD	27
Flunixin meglumide	5.0	IM	Single injection	Mallard ducks	12-h activity but muscle necrosis at injection site	PD	28
	5.5	IM	24 for 7 days	Budgerigars	Severe renal lesions	TOX	29
	1.1	IV	Single injection	Chickens, ostrich, ducks, turkeys, pigeons	Chickens had long half-life but 10 min $t_{1/2}$ in ostrich	PK	25
	3	IM	Single injection	Chickens	Arthritis painful behaviors reduced 1 h after treatment	PD	24

Ketoprofen	2.0	IV, IM, oral	Single injection	Quail	Low bioavailability IM, orally. Short IV $t_{1/2}$	PK	30
	12	IM	Single injection	Chickens	Arthritis painful behaviors reduced 1 h after treatment	PD	24
	2.5	IM	24 for 7 days	Budgerigars	Renal tubular necrosis	TOX	29
	5	IM	Single injection	Mallard ducks	12-h activity	PD	28
	2.0	Oral	12–24	Eiders	Mortality associated with male eiders	CS	31
	5.0	IM, IV					
Meloxicam	1	IM	12	Hispaniolan Amazon parrots	Improved weight bearing on arthritic limb	PD	32
	0.1	IM	24 for 7 days	Budgerigars	Renal glomerular congestion	TOX	29
	0.5	IV	Single injection	Chickens, ostrich, ducks, turkeys, pigeons	Variable distribution, slow clearance except ostrich	PK	25
	2	IM, oral	Single treatment	Cape Griffon vultures	Short $t_{1/2.}$ less than 45 min	PK	33
Piroxicam	0.5–0.8	Oral	12	Whooping cranes	Used for acute myopathy and chronic arthritis	CS	J. Paul-Murphy, personal communication, July 1, 2010

Abbreviations: ASA, acetylsalicylic acid (aspirin); CS, care report or case series; IM, intramuscularly; IV, intravenously; PD, pharmacodynamic; PK, pharmacokinetic; TOX, toxicity; $t_{1/2}$, half-life.

contribute to postoperative pain. This noxious stimulus-induced sensitization can be prevented or preempted by administration of analgesic agents before tissue injury. This concept is being applied clinically with increasing frequency. Preemptive analgesia with opiates, NSAIDs, and/or local anesthetics can block sensory noxious stimuli from onward transmission to the CNS, thus reducing the overall potential for pain and inflammation, and potentially improving the patient's short-term and long-term recovery.

OPIOIDS

Opioids are used for moderate to severe pain, such as traumatic or surgical pain. Opioids reversibly bind to specific receptors in the central and peripheral nervous system. These drugs are categorized as either agonists, partial agonists, mixed agonist/antagonists, or antagonists based on their ability to induce an analgesic response once bound to a specific receptor. These drugs may be agonists at one receptor type and display antagonist or partial agonist effects at another receptor type. The agonist drugs have a linear dose-response curve that may be titrated to reach the desired effect, whereas the agonist/antagonist drugs may reach a ceiling effect after which increasing the dose does not seem to provide additional analgesia. During anesthesia, opioids are used to provide perioperative analgesia that may reduce the concentrations of volatile anesthetics (ie, gas anesthesia-sparing effects). The most common adverse effects reported with opioids are cardiac and/or respiratory depression. In many cases, these drugs may be reversed with antagonists, which will also terminate analgesia. The application and doses of several opioid formulations have been scientifically evaluated and clinically applied in birds (see **Table 1**).

Most opioid analgesics are used parenterally because of poor oral bioavailability associated with the first pass effect. Once absorbed, oral opioids first pass through the liver where they are metabolized, releasing a significantly lower amount of active drug into the general circulation. For example, the bioavailability of 5 mg/kg orally administered butorphanol in Hispaniolan Amazon parrots (*Amazona ventralis*) was less than 10% making this route ineffective (see **Table 1**).[12]

Opioids vary in their receptor specificity and efficacy in mammals, which results in a wide variety of clinical effects in different species. It is reasonable to presume that this opioid variability will also have a wide range of clinical effects in avian species. The distribution of opiate receptor types is well conserved across all mammalian species in the brainstem and spinal cord, but may vary markedly in the forebrain and midbrain. However, even with receptor distribution information in some species, it is still difficult to draw firm conclusions regarding the functional roles of different opioid receptor types because the physiologic and clinical effects of opioids may be influenced by pharmacologic variables such as the commercial preparation of opioid and the dose and route of administration, as well as by individual variables such as whether the animal has been stressed, injured, or anesthetized. There is an overall lack of published data concerning differences in opioid receptor distribution, density, and functionality in birds. In pigeons, the regional distribution of μ, κ, and δ receptors in the forebrain and midbrain were similar to mammals but the κ and δ receptors were more prominent in the pigeon forebrain and midbrain than μ receptors and 76% of opiate receptors in the forebrain were determined to be κ-type.[35] κ receptors have multiple physiologic functions in the bird and the analgesic function of these receptors still needs further investigation. It has been postulated that this difference in receptor distribution and density may partially explain why birds do not seem to respond to μ agonists in the same manner as mammals. However, in day-old chicks, marked dissimilarities to this distribution suggest either age- or species-related differences. It has been postulated that birds may not possess distinct μ and κ receptors or that the receptors may have similar functions. This may explain in part why the isoflurane-sparing effects of μ and κ agonists in chickens seemed to be similar to mammals.[36]

OPIOID FORMULATIONS

Morphine is a μ receptor agonist and has not been commonly used in avian medicine. Studies on domestic fowl have demonstrated confusing results on clinical doses. For example, morphine produced analgesia at high doses (200 mg/kg) in chicks in 1 early study using 1 testing strategy,[37] whereas later studies demonstrated analgesia with morphine in chicks at doses that approximate the analgesic dose range used in other species, however the results were sometimes conflicting.[2,38] Differing analgesic responses to morphine have also been detected between strains of chickens[39] including 1 study that showed analgesic effects in 1 strain at a given dose, whereas 2 other strains exhibited a hyperalgesic response with the same dose.[2] A study evaluating intraarticular injection of 1 to 3 mg morphine in a domestic fowl arthritis model found no significant antinociceptive effects but it is unclear whether pH differences in synovial fluid may have affected the activity of the drug.[20]

Fentanyl is a short-acting μ receptor agonist that has not been commonly used in avian medicine because historical investigations with morphine (the standard for μ opioids) administered to chickens were confusing and clinically inconclusive. Fentanyl 0.02 mg/kg intramuscularly (IM) did not affect the withdrawal thresholds to electrical or thermal stimuli of white cockatoos,[18] however, a tenfold increase in the dose (0.2 mg/kg subcutaneously [SC]) did produce an analgesic response, but many birds were hyperactive for the first 15 to 30 minutes after receiving the high dose.[18] Fentanyl had rapid absorption and elimination in parrots, with mean residence times of less than 2 hours (see **Table 1**).[18] Because of its short-acting properties, fentanyl delivered via constant-rate infusion (CRI) is an excellent choice as an analgesic adjunct to inhalant anesthesia in mammals and when used at low doses as a CRI, the authors have found fentanyl may also be effectively used in avian anesthetic protocols. Fentanyl administered as an intravenous (IV) CRI in red-tailed hawks (*Buteo jamaicensis*) to target plasma concentrations of 8 to 32 ng/mL reduced the minimum anesthetic dose (MAD) of isoflurane 31% to 55% in a dose-related manner, without statistically significant effects on heart rate, blood pressure, Pa_{CO_2}, or Pa_{O_2}.[19] Fentanyl may also be combined with ketamine as a CRI thereby reducing the required doses of each.

Butorphanol is a mixed agonist/antagonist with low intrinsic activity at the μ receptor and strong agonist activity at the κ receptor. There is some evidence to suggest that butorphanol does not produce dose-related respiratory depression in contrast to μ receptor agonists. Adverse effects associated with butorphanol such as dysphoria have not been reported in birds. Preoperative butorphanol administration (2 mg/kg IM) did not show significant anesthetic (including time to intubation and extubation) or cardiopulmonary changes in Hispaniolan Amazon parrots anesthetized with sevoflurane, suggesting that it may be useful as part of a preemptive analgesic protocol (see **Table 1**).[17] Earlier isoflurane-sparing studies using 1 mg/kg IM butorphanol in cockatoos, African gray parrots (*Psittacus erithacus erithacus*), and blue-fronted Amazon parrots (*Amazona aestiva*) showed a significant reduction in the MAD for the cockatoos and African gray parrots, but not for the blue-fronted Amazon parrots, which indicates species variability at that dose of butorphanol (see **Table 1**).[14,15] In a study using withdrawal thresholds to electrical stimuli in conscious African gray parrots, butorphanol at 1 to 2 mg/kg showed a decreased withdrawal effect that was more significant at 2 mg/kg (see **Table 1**).[16] Butorphanol doses of 3 and 6 mg/kg IM had similar analgesic effects on Hispaniolan Amazon parrots (see **Table 1**).[16] Doses of 3 mg/kg demonstrated significant analgesia, but increasing the dose to 6 mg/kg did not increase the effect.[16] Based on these studies, doses of 1 to 4 mg/kg have been suggested in birds but empirical dosing frequencies ranging from 2 to 24 hours have been published. A recent study evaluating the PK of 0.5 mg/kg butorphanol in red-tailed hawks (*Buteo jamaicensis*) and great-horned owls (*Bubo virginianus*) found half-lives of 0.93 and 1.78 hours, respectively when given IV and 0.94 and 1.84 hours, respectively when given IM (see **Table 1**).[11] Likewise, low serum butorphanol concentrations were evident in Hispaniolan Amazon parrots 2 hours after single IM administration of a 5 mg/kg dose (see **Table 1**).[13] These data suggest that frequent dosing of butorphanol may be necessary in birds. This frequency of dosing is in some cases impractical because of lack of personnel to provide frequent dosing and the stress of frequent handling on the patient. A liposome-encapsulated, long-acting form of butorphanol tartrate was recently shown to be safe and effective in Hispaniolan parrots for up to 5 days following SC administration,[13] and was also shown to be an effective analgesic in Hispaniolan Amazon parrots and green-cheeked conures (*Pyrrhura molinae*) with induced arthritis.[26,34] The results from these studies are encouraging because a long-acting formulation of butorphanol would allow for both reduced frequency in butorphanol dosing and handling of avian patients for drug administration. Unfortunately, this formulation is not yet commercially available.

Buprenorphine is a slow-onset, long-acting opiate with a unique and complex pharmacologic profile. Buprenorphine is believed to act as a partial μ agonist but its κ receptor activities are less well defined. Several studies suggest that buprenorphine demonstrates κ receptor agonist effects but other evidence in mammals and pigeons suggests that it also displays some κ antagonistic activities. Buprenorphine has unusual receptor-binding characteristics that seem to be the result of slow drug dissociation from opioid receptors. Buprenorphine may exhibit a plateau or ceiling analgesic effect; increased doses may result in no additional analgesia, or may have detrimental effects. Few studies have been published evaluating the use of buprenorphine in birds. One study evaluating 0.05 to 1.0 mg buprenorphine administered intra-articularly in a domestic fowl arthritis model found no significant antinociceptive effects but it is unclear whether differences in the pH of synovial fluid may have affected the activity of the drug.[20] Buprenorphine at 0.1 mg/kg IM in African gray parrots did not have an analgesic effect when tested by PD analgesimetry, but PK analysis suggests this dose did not achieve plasma concentrations effective for humans (see **Table 1**).[16,21] Pigeons given 0.25 and 0.5 mg/kg IM buprenorphine had an increased latency period for withdrawal from a noxious electrical stimulus of 2 and 5 hours, respectively.[22] Further work is required to determine whether clinical efficacy may be obtained using different buprenorphine doses in other avian species.

Nalbuphine hydrochloride exerts its agonist activity principally at the κ receptor and is a partial antagonist at the μ receptor. It is used as an analgesic in the treatment of moderate to severe pain in humans and has a relatively lower incidence of respiratory depression that does not increase with additional dosing. Nalbuphine hydrochloride was rapidly cleared after both IM and IV dosing of 12.5 mg/kg to Hispaniolan Amazon parrots and had excellent bioavailability following IM administration, with little sedation and no adverse effects (see **Table 1**).[40] The same dose increased threshold values of thermal foot withdrawal in this species for up to 3 hours; higher doses (25 and 50 mg/kg IM) did not significantly increase the withdrawal threshold values above those of the 12.5 mg/kg dose.[23] Because of its low abuse potential, this opioid is currently not a Drug Enforcement Administration scheduled substance. Based on the receptor activity of this drug, and its potential for minor to few side effects, nalbuphine hydrochloride may show promise as an analgesic in pain management protocols in avian patients.

NSAIDs

NSAIDs are the most common class of analgesic drugs prescribed in small animal medicine. NSAIDs are used to relieve musculoskeletal and visceral pain, acute pain, and chronic pain such as osteoarthritis. The pharmacologic activity of NSAIDs has been reviewed in veterinary articles and textbooks and although most reviews do not consider avian applications, it is assumed that the chemistry and mechanism of action is similar when administered to birds.[41,42] A broad tissue distribution of cyclooxygenase (COX) has been demonstrated in chickens.[43] The relative expression of COX-1 and COX-2 enzymes varies between species and both enzymes are important in avian pain, but more information is needed to differentiate their physiologic effects in avian species.

The application and doses of several NSAID formulations continues to be scientifically evaluated as well as clinically applied in birds (see **Table 2**). As new NSAID formulations appear on the human and veterinary pharmaceutical market, the off-label use of these drugs in birds will be apparent. The intention of recently developed NSAIDs has been to spare COX-1 and emphasize COX-2 inhibition with the goal of providing analgesia and suppressing inflammation without inhibiting physiologically important prostaglandins. The common NSAIDs used in avian medicine at the time of this writing include meloxicam, carprofen, ketoprofen, celecoxib, and piroxicam, each with a distinct COX-1/COX-2 ratio and differing reports of effectiveness and toxicity in birds.

The selection of NSAID is determined by the ease of administration best suited to the situation; for example, giving an injectable formulation at the time of surgery, followed by oral formulation of the same or different NSAID postoperatively. There is little scientific support for a washout period when switching NSAIDs.[41] In cases of acute or chronic pain there may be a benefit to changing the NSAID and a washout period could put the bird at risk of having untreated pain. Only 1 NSAID should be used at a time, but in cases of chronic pain the response to therapy needs to be frequently reevaluated and the NSAID may need to be changed or augmented with other analgesics if response is poor or diminishing.

To evaluate the analgesic efficacy of an NSAID for avian species, several criteria need to be considered. The dose and frequency of NSAID administration depends on PD evaluations as well as PK data. Plasma levels are not sufficient information to predict the physiologic activity of the NSAID. Antiinflammatory and analgesic effects of NSAIDs continue longer than predicted by plasma half-lives. One explanation for the long duration of effect is the high protein binding, such as the protein in an inflamed site, which acts as a reservoir for the drug after it has been eliminated from the plasma.[44] This leads to persistence of the NSAID in inflamed sites longer than in the plasma. An alternate explanation is possible biotransformation of NSAIDs leading to active metabolites not being measured, however, metabolism of most NSAIDs in mammalian species occurs in the liver and the metabolites are generally inactive, and it assumed to be similar in avian species. Most NSAIDs are weak acids that are highly protein bound and most have a small volume of distribution. There are tremendous species differences in drug elimination among the NSAIDs.

The best example of avian species variability is the PK study of meloxicam, flunixin, and sodium salicylate administered intravenously to chickens, ostriches (*Struthio camelus*), mallard ducks (*Anas platyrhynchos*), turkeys (*Meleagris gallopavo*), and pigeons (*Columba livia*).[25] All 3 NSAIDs were rapidly eliminated in these species, however the volume of distribution was highly variable, which may reflect species differences in protein binding. Allometric analysis of the NSAID data in these 5 species concluded that despite renal filtration of the drugs, allometry is not useful for extrapolation of doses between avian species.[25] Although the distribution, half-life, and clearance have been characterized for some NSAIDs in a few species of birds, this information has not always been of use for predicting safe and effective dose regimens.

Presently accepted PD NSAID studies measure inhibitory concentrations of COX-1 and COX-2 concurrent with the PK of the drug to derive the clinically optimal and safe doses for animals, but these studies have not been done in any avian species. However, PD studies have been published describing the effects of ketoprofen and flunixin on thromboxane B2 (TBX) concentrations in mallard ducks.[28] Because NSAIDs block binding of arachidonic acid with COX enzyme, preventing conversion to TBX, plasma TBX is used to estimate the duration of NSAID action. In mallard ducks, flunixin (5 mg/kg) and ketoprofen (5 mg/kg) suppressed TBX levels for up to 12 hours, suggesting that their physiologic action may be that long.[28,45] A field study using ketoprofen in mallard ducks demonstrated analgesic effects but noted that the onset of analgesic effects may be longer than 30 minutes in some ducks.[45]

In vivo measurements use analgesimetry to evaluate the effect of an NSAID under physiologic and pathologic conditions and predict clinical outcome. Several analgesimetry models have been used to evaluate the PD of NSAIDs in chickens. Dose responses for carprofen, flunixin, ketoprofen, and sodium salicylate for treatment of inflammatory pain were determined in chickens using the articular pain model to measure the effect on specific behaviors.[24] Sodium salicylate was determined to be less effective than the other NSAIDs and large doses of carprofen were needed to return to nonarthritic behaviors; minimum effective doses determined in this study are listed in **Table 2**. A similar experimental arthritis model in parrots (*Amazona ventralis*) was used to evaluate NSAID treatment by measuring the return to normal weight bearing.[26,32] Carprofen (2 mg/kg IM every 12 hours) was less effective than butorphanol to improve weight bearing on the arthritic limb in parrots.[26] Alternatively, in a similar study, meloxicam (1 mg/kg IM every 12 hours) was effective at returning the parrots to normal weight bearing on the arthritic limb throughout the 36 hours of observation.[32]

ADVERSE EFFECTS OF NSAIDs

The most common adverse actions of NSAIDS in mammals include effects on the gastrointestinal system, renal system, and coagulation. NSAIDs have recently been implicated in humans and mammals with an increased risk of myocardial infarction and delays in bone healing,[46,47] but these effects have not been substantiated in birds. However, it is prudent to be aware that these adverse effects are often dose dependent and associated with chronic administration. The most common adverse effect of NSAIDs reported in avian species is the effect on renal tissue and function.

Prostaglandins in the kidney have an important role in regulating water and mineral balances and modulating intravascular tone. The kidney uses both COX-1 and COX-2 for prostaglandin synthesis and injury occurs when renal prostaglandin synthesis is inhibited. Originally it was hypothesized that the adverse renal effects of NSAIDs were linked primarily to COX-1 inhibition, however COX-2–selective NSAIDs may also have a significant risk of inducing adverse effects. COX-2 is constitutively expressed in the kidney in chickens, similar to all mammalian species studied and is highly regulated in response to alterations in intravascular volume.[43] COX-2 metabolites have been implicated in the maintenance of renal blood flow, mediation of renin release, and regulation of sodium excretion. Therefore, in conditions of relative intravascular volume depletion and/or renal hypoperfusion such as dehydration, hemorrhage, hemodynamic compromise, heart failure, and renal disease, interference with COX-2 activity can have significant deleterious effects on renal blood flow and glomerular filtration rate. In a study using northern bobwhite quail (*Colinus virginianus*), birds were treated for 7 days with a range of flunixin meglumine doses and even the lowest dose (0.1 mg/kg) caused glomerular lesions.[48] When budgerigars were treated with 5.5 mg/kg flunixin meglumine, 2.5 mg/kg ketoprofen, or 0.1 mg/kg meloxicam for either 3 or 7 days, plasma uric acid and protein levels did not change but a low frequency of glomerular congestion, degeneration, and dilation of tubules occurred.[29] Lesions were more severe in birds treated with flunixin meglumine for 3 or 7 days with increased mesangial matrix synthesis.[29]

The recent massive mortalities in 3 vulture species on the Asian subcontinent led to banning of the NSAID diclofenac (DF) on the Indian subcontinent. Common findings of diffuse visceral gout and proximal convoluted tubular damage indicated that the site of toxicity was the kidneys or the renal supportive vascular system.[49,50,51,52] The association of DF with vulture mortalities led to several investigations to establish the mechanism of toxicity for DF and other NSAIDs in several avian species. The effect of DF on inhibition of renal prostaglandins and subsequent closure of the renal portal valves was proposed to cause severe renal ischemia and nephrotoxicity.[51] But recent studies determined that vulture susceptibility to DF results from a combination of an increased reactive oxygen species (chemically reactive molecules containing oxygen such as oxygen ions and peroxide), interference with uric acid transport, and the duration of exposure.[50] Both DF and meloxicam were found to be toxic to renal tubular epithelial cells following 12 hours of cell culture exposure, caused by an increase in production of reactive oxygen species; in cultures incubated with either drug for only 2 hours, meloxicam showed no toxicity in contrast to DF.[50] DF also decreased the transport of uric acid, by interfering with the *p*-amino-hippuric acid channel. In addition, the half-life of DF in vultures (14 hours) is much longer than chickens (2 hours) thus exposing vultures to toxic effects of DF for prolonged time periods.[50]

NSAID FORMULATIONS

Ketoprofen is a potent nonselective COX-1 inhibitor that has been used extensively in small animal medicine. The excellent oral bioavailability of ketoprofen in mammals makes this drug attractive for oral dosing. However, ketoprofen is most commonly used parenterally in birds because of limited oral PK data and difficulty in accurately dosing the oral formulation in small species. PK studies evaluating a single dose of 2 mg/kg ketoprofen given orally, IM, and IV in Japanese quail (*Coturnix japonica*) showed very low oral (24%) and IM (54%) bioavailability of the drug, and the shortest half-life reported for this NSAID in any species.[30] Although it is possible that drug formulation could account for the low bioavailability of the drug in this study, additional studies are needed to determine whether drug formulations or physiologic differences between species could account for these differences. PD studies of 5 mg/kg IM ketoprofen in mallard ducks (*Anas platyrhynchos*) found an overall decrease in the inflammatory mediator TBX for approximately 12 hours after administration.[28] This suggests that the duration of the antiinflammatory effect in the mallards may parallel that of some mammals studied, therefore further studies in additional species are necessary to evaluate the duration of effect and bioavailability of this drug in birds. When ketoprofen (2 to 5 mg/kg IM) was administered to free-ranging spectacled eiders (*Somateria fischeri*) and king eiders (*Somateria spectabilis*), 4/10 male spectacled eiders and 5/6 male king eiders died within 1 to 4 days after surgery.[31] The histologic findings included severe renal tubular necrosis, acute rhabdomyolysis, and mild visceral gout. Strong consideration was given to the male behaviors during the mating season that may have predisposed these birds to dehydration and the adverse effects of COX inhibition.[31]

Carprofen can be administered parenterally or orally and is well absorbed through the gastrointestinal tract in mammals. The mechanism of action of carprofen has not been fully elucidated. It is a weak inhibitor of COX at therapeutic doses and yet exhibits good antiinflammatory activity. This weak inhibition of both COX isoforms may explain its wide margin of safety compared with other NSAIDs and it may achieve its therapeutic effects partially through other pathways.[53] Carprofen given SC significantly improved the speed and walking ability of lame chickens in a dose-dependent manner[27] An extremely high dose of carprofen of 30 mg/kg IM was needed for analgesia in chickens with experimental arthritis[24]; this dose is 6 to 10 times higher than standard mammal doses. An analgesia study in Hispaniolan Amazon parrots with experimental arthritis noted that 2 hours after carprofen administration, lameness was markedly improved but the analgesic effect was very short-term because 3 mg/kg IM of carprofen every 12 hours did not significantly improve the weight-bearing load of the arthritic limb for the 30-hour study period.[26] It was noted that 2 hours after carprofen administration, the lameness was markedly improved but the analgesic effect was very short-term.[26] Much work is needed to determine appropriate doses, dosing routes, and dosing frequency of carprofen in birds.

Meloxicam is a COX-2 selective oxicam NSAID. In recent years, meloxicam has become the most widely used antiinflammatory medication in exotic animal practice. A survey to determine NSAID toxicity in captive birds treated in zoos reported zero fatalities associated with meloxicam, which was administered to more than 700 birds from 60 species.[54] Ostriches given meloxicam IV exhibited the most rapid half-life (0.5 hours) compared with ducks, turkeys, pigeons, and chickens.[25] Meloxicam is currently available as an oral suspension and an injectable form. A dose-response analgesia study with Hispaniolan Amazon parrots with experimental arthritis determined that 1 mg/kg of meloxicam IM every 12 hours was necessary to achieve significant return to baseline weight bearing.[32] Oral administration of 1 mg/kg of meloxicam suspension to Hispaniolan Amazon parrots had lower bioavailability than when administered parenterally, and the highest mean concentration expected to provide analgesia was 6 hours after administration.[55] Japanese quail were treated with 2mg/kg of meloxicam IM for 14 days and the changes in complete blood count and serum chemistry parameters were minimal; the histologic changes in the kidney were unremarkable.[56] Clinical recommendations for treatment of parrots with high doses of meloxicam needs critical examination of its effect on renal parenchyma. Future studies to evaluate PD-PK of meloxicam administered by different routes in different avian species is necessary to determine appropriate analgesic doses and dosing schedules for meloxicam in avian patients.

Piroxicam is a nonselective NSAID used for its antiinflammatory properties as well as its value as a chemopreventative and antitumor agent. It has a much higher potency against COX-1 than COX-2. Piroxicam has good oral bioavailability and a long half-life in mammals but PD and PK studies have not been done in any avian species. Despite the high incidence of the negative side effects of piroxicam used in humans, there are no reports of its toxicity in birds. It has been used clinically for long-term treatment of chronic arthritis in cranes.[57]

REGIONAL ANESTHESIA AND ANALGESIA

In all vertebrates, including birds, local anesthetics block sodium channels in the nerve axon, interfering with the generation and conduction of action potentials along the nerve. When local anesthetics are used preemptively, the number and frequency of impulses are reduced, thereby reducing nociceptor sensitization, which has the beneficial effect of minimizing central sensitization. Regional infiltration using a local line or splash block is the most common method. The subcutaneous space in most avian species is very thin so a small-gauge needle is recommended to make several SC injections into the operative area. Lidocaine and bupivacaine have been used for brachial plexus blockade in a variety of avian species but a recent evaluation of bupivacaine (2 and 8 mg/kg) and lidocaine with epinephrine (15 mg/kg) found neither to effectively block nerve transmission in the brachial plexus of mallard ducks,[58] which was similar to the significant failure rate reported when studied in chickens.[59] Local anesthetics in the form of transdermal patches and creams, epidural infusions, spinal blocks, and intravenous blocks have not been reported.

Local anesthetics are absorbed by the vasculature in the region being blocked. Systemic uptake of the local anesthetics can be rapid in birds, and metabolism may be prolonged, increasing the potential for toxic reactions. The duration of action depends on the molecular properties and lipid solubility of the drug. Neither the time to effect nor duration of action has been determined in birds. Dosage recommendations are lower for birds than mammals because birds may be more sensitive to the effects of the drug. Chickens given intraarticular injections of high doses of bupivacaine (2.7 to 3.3 mg/kg) showed immediate signs of toxicity such as drowsiness and recumbency.[60] Other toxic effects reported in birds include fine tremors, ataxia, recumbency, seizures, stupor, cardiovascular effects, and death. Toxic effects can be acute if accidentally injected intravenously.

Lidocaine is available as a commercial preparation of 2% (20 mg/mL) and the formulation without epinephrine is recommended. Based on empirical use, the recommended dose is 2 to 3 mg/kg, although 15 mg/kg with epinephrine had no adverse effects when used for brachial plexus block in mallard ducks.[58] For small birds, the commercial preparation may need to be diluted 1:10 or more to achieve an effective volume for the block. It is unknown whether this dilution provides either the appropriate tissue drug levels for analgesia or the expected duration of analgesia.

Bupivacaine is the most clinically useful perioperative local anesthetic in mammals because it is a long-acting local anesthetic. The commercial preparations of bupivacaine available are 0.25%, 0.5%, and 0.75% solutions (2.5, 5, 7.5 mg/mL, respectively), and the lower concentration may not need dilution for birds. It has been used conservatively in birds because of concerns that toxic effects may take longer to resolve as a result of this drug's longer duration of effect. The recommended maximum dose of bupivacaine for mammals is 2 mg/kg, however results from a study in which mallard ducks (*Anas platyrhynchos*) were given bupivacaine (2 mg/kg SC) suggested that bupivacaine may be shorter acting in ducks than in mammals.[61] In this study, bupivacaine showed a faster absorption versus elimination rate, and sequestration and redistribution of bupivacaine was suggested by increases in plasma concentrations at 6 and 12 hr after administration making it possible for toxicity to be delayed. Higher doses of 8 mg/kg had no adverse effects when used for brachial plexus block in ducks.[58] Intraarticular bupivacaine (3 mg in 0.3 mL saline) was effective for treating arthritic pain in 1.5-kg chickens.[60] A 1:1 mixture of bupivacaine and dimethyl sulfoxide was applied to amputated chicken beaks immediately after amputation and feed intake was improved.[62]

OTHER ANALGESICS

Tramadol hydrochloride is an analgesic that has become popular recently despite minimal evidence as to its efficacy. It is active at opiate, alpha-adrenergic, and serotonergic receptors.[63] Tramadol is a weak μ agonist but the *O*-desmethyl metabolite (M1) is a much more potent agonist in mammals. Other metabolites including M2-M5 have also been described but their analgesic properties, if any, are not yet known. The conversion to the M1 metabolite is variable among species but it is known that it is produced in bald eagles, red-tailed hawks, (Souza MJ, personal communication, July 1, 2010) and Hispaniolan Amazon parrots.[64,65] It is available in oral and injectable formulations and currently the drug is not a controlled substance. In humans, less respiratory depression and constipation are seen with tramadol than with μ agonist opioids, but there are no data to date for other species. The oral (11 mg/kg) and IV (4 mg/kg) pharmacokinetics of single-dose tramadol have been evaluated in bald eagles[65] but analgesic plasma concentrations for tramadol and its M1 metabolite have not yet been established. Oral bioavailability of tramadol (mean $\pm$ SD = 97.94 $\pm$ 0.52%) was higher than that observed in humans and dogs, suggesting this as a useful route of administration in this species. Tramadol 11 mg/kg administered orally achieved concentrations in the human analgesic range for 10 hours in 5/6 bald eagles; M1 plasma concentrations reached the human range only in 2 eagles at much earlier time points.[65] The $t_{1/2}$ of tramadol in bald eagles after oral dosing was 2 times that reported in dogs, but half as long as in humans.[65] Until specific analgesic plasma concentrations are known, it is difficult to predict how these differences may affect appropriate dosing frequency after repeated doses. Mild transient bradycardia was observed immediately after IV administration in 3/6 birds, but was not considered clinically significant.[65] Although this analgesic holds great promise for use in birds, much work is still needed to evaluate appropriate dosing, efficacy, and safety of this drug in different species.

Gabapentin**,** a γ-aminobutyric acid analogue, has been used to treat neuropathic pain in humans for almost a decade. Its exact mechanism of action is unknown, but its therapeutic action on neuropathic pain is believed to involve voltage-gated N-type calcium ion channels. To date, there is only 1 published report and 2 proceedings articles on the clinical use of gabapentin as part of a multimodal therapeutic plan for suspected neuropathic pain in birds.[66,67,68] In all 3 reports, self-mutilation appeared to be relieved after the addition of gabapentin to the therapeutic regime.

BALANCED OR MULTIMODAL ANALGESIA

Combinations of drugs acting at different points in the nociceptive system provide a greater effect and potentially less toxicity than individual drugs given alone. For example, opioids generally act centrally to limit the input of nociceptive information into the CNS, whereas NSAIDS generally act peripherally to decrease inflammation thus limiting the nociceptive information that initially enters the CNS. Balanced analgesia with opiates, NSAIDS and/or local anesthetics administered before a painful procedure can block sensory noxious stimuli from onward transmission to the CNS, thus reducing the overall potential for pain and inflammation. These synergies have been demonstrated in laboratory animals and are now being used in the clinical environment. Balanced analgesia should be considered in virtually every avian patient as the use of multimodal therapy may maximize analgesic efficacy and minimize individual drug toxicity in these patients for which few analgesic data are available.

SUMMARY

Avian analgesia is now recognized as a critical component of avian medicine and surgery. The need to recognize pain and to provide pain relief is the first step, and many anecdotal therapeutic doses have been extrapolated from other companion animals. Several published research investigations, using several species of birds, have begun to provide avian analgesia therapeutic information for clinical application. The challenge is to continue pushing this research forward with appreciation that there are approximately 10,000 known species of birds, perhaps 200 species commonly kept as pets, and that each species has a range of behaviors as varied as their species-specific PKs and PDs for each analgesic drug.

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